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Original Article

ENVIRONMENTALLY BENIGN SYNTHESIS OF N'-SUBSTITUTED NAPHTHALENE-1-SULFONOHYDRAZIDE UNDER MICROWAVE IRRADIATION AND THEIR BIOLOGICAL EVALUATION

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ABSTRACT

Objective: Microwave synthesis provides an alternative environmentally benign method with excellent yield and shorter reaction time. The aim of this study is to synthesize some new sulfonohydrazide derivatives by conventional/microwave method and their antimicrobial evaluation.

Methods: Condensation of naphthalene-1-sulfonohydrazide with aromatic carbonyls under Conventional refluxing/microwave irradiation.

Results: A facile, rapid and eco-friendly synthetic route for the synthesis of new sulfonohydrazide derivatives by microwave irradiation method was reported. Structures of the newly synthesized compounds were elucidated by elemental analysis and spectral studies viz. IR, NMR and MS. These compounds showed good to excellent antimicrobial activity against tested microbial strains. The zone of inhibition and minimum inhibitory concentration values for tested microbial strains was in range of 10-14 mm and 6.25-25µg/ml.

Conclusion: A novel series of biologically active N′-substituted naphthalene-1-sulfonohydrazide derivatives were synthesized by green method. Most of the newly synthesized compounds showed good to excellent antimicrobial activity.

Keywords: Hydrazones, Condensation, Microwave irradiation, Antimicrobial activity.

INTRODUCTION

Hydrazones are important class of compounds in organic chemistry. These compounds have interesting biological properties [1] such as antipyretic [2], analgesic [3], anti-inflammatory [4], antituberculosis [5-11], anticonvulsant [12], antimicrobial and anticancer [13]. A number of hydrazone derivatives have also been used as herbicides, insecticides, nematocides, rodenticides and plant growth regulators [14] as well as plasticizers and stabilizers for polymers [15,16]. Hydrazones are important compounds for drug design [17] as possible ligands for metal complexes [18], organocatalysis [19] and synthesis of heterocyclic rings [20]. The synthetic efforts for this class of compounds are very well studied and generally entail the reaction of carbonyl compounds with hydrazine hydrate in organic solvents [21]. Some important methods for the synthesis of hydrazone in the presence of $ZnCl_2$ [22], $TiCl_2$ [23], $MgSO_4$-PPTL [24], $Mg(ClO_4)_2$ [25], K-10 [26] and SiO_2-$NaHSO_4$ [27] catalysts are also reported. For the synthesis of hydrazones most of the reaction methods described involve several hour refluxing with the use of methanol/ethanol as solvent. In recent years organic reactions under solvent free conditions have gained popularity [28], since the majority of solvents are either toxic or inflammable and considerably enhance the cost of the overall synthesis. Therefore, solvent-free reactions significantly reduce reaction time and make the work up easier [29, 30]. Thus we have demonstrated an efficient and rapid environmentally benign method.

MATERIALS AND METHODS

All commercially available chemicals and reagents were purchased from Sigma Aldrich, Merck and HIMEDIA. Melting points were recorded in open capillaries and were uncorrected. IR spectra were recorded on a FTIR-8400S SHIMADZU spectrophotometer by using KBr. ^1H and ^{13}C NMR spectra were recorded on Bruker's NMR spectrophotometer at 300MHz and 75MHz respectively in $CDCl_3$/DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts were given in δ (in ppm) relative to the TMS with coupling constant (J) in Hz. Mass Spectra were measured on Water's mass spectrometer. Elemental analysis was carried out on a Perkin Elmer CHNS/O Analyzer 2400. The progress of the reaction was monitored through TLC using precoated silica aluminium plates (Merck Silica gel $^{60}F_{254}$) and spots were visualized by ultraviolet lights irradiation (254 nm*) or by exposure to iodine vapors. Column chromatography was performed over silica gel (Merck, particle size 60-120 mesh) using n-hexane: ethyl acetate 7:3 mixture as eluting agent.

General procedure for the Synthesis of N′-(substituted benzylidene) naphthalene-1-sulfonohydrazide (3a-j)

Conventional method

A mixture of naphthalene-1-sulfonohydrazide **1** (1 mm*ol) and aromatic carbonyls 2a-j (1 mm*ol) in ethanol (10 mL) was refluxed for 3-6 hours respectively with continuous stirring. A catalytic amount of acetic acid is added to reaction mixture and the progress of the reaction was monitored through TLC. The resulting compound was concentrated in a rotatory evaporator. The crude product was purified by column chromatography using silica gel as solid support and n-hexane: ethyl acetate (7:3).

Green method

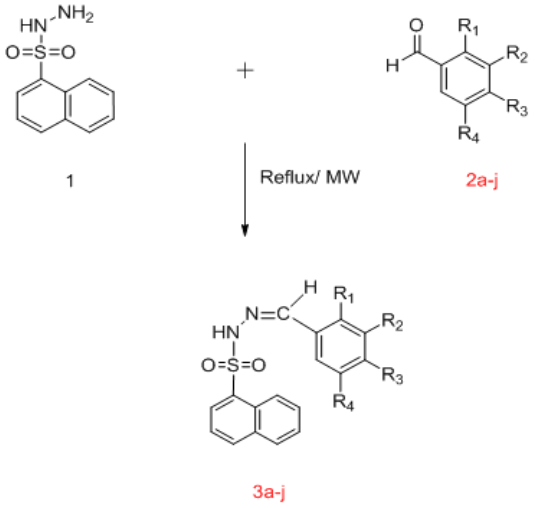
A mixture of naphthalene-1-sulfonohydrazide **1** (1 mm*ol) and aromatic carbonyls 2a-j (1 mm*ol) was ground with silica gel (Merck, particle size 60-120 mesh) in a mortar and pestle at room temperature. The homogenized mixture was then exposed to microwave irradiation at 100 ^{0}C in a closed vessel for 3-5 min with intermittent cooling at every 30 second. The progress of the reaction was monitored through TLC. On completion of the reaction (as indicated by TLC), the reaction mixture was cooled to room temperature, triturated with ethyl acetate and filtered through a small plug of cotton. The ethyl acetate layer was evaporated and the crude product was recrystallized from ethanol to get pure products.

Spectral data

N′-(4-methoxybenzylidene)naphthalene-1-sulfonohydrazide (3a)

Red solid, mp 145-147 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3265 (NH), 3045 (Ar-H), 2868 (=CH), 1628 (C=N), 1370, 1160 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.78 (s, 3H, OCH_3), 7.32-7.99 (m, 7H, Ar-H), 7.39 (d,

2H, Ar-H, *J* 8.1), 7.80 (d, 2H, Ar-H, *J* 8.1), 7.73 (s, 1H, -N=CH-Ar), 8.80 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 55.3 (-OCH_3), 114.2-154.13 (Ar-C), 148.53(HC=N). MS (ESI, 70 eV) m/z: 341 (M^++1). $C_{18}H_{16}N_2O_3S$. Calculated, % C 63.51, H 4.74, N 8.23. Found, % C 63.45, H 4.79, N 8.28.



Scheme 1: Synthesis of hydrazones under microwave irradiation

N′-(2,4-dimethoxybenzylidene)naphthalene-1-sulfonohydrazide (3b)

Red solid, mp 152-154 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3270 (NH), 3040 (Ar-H), 2970 (=CH), 1620 (C=N), 1340, 1125 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.73 (s, 6H, OCH_3), 6.32-7.92 (m, 10H, Ar-H), 8.02 (s, 1H, -N=CH-Ar), 9.02 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 58.5 (2-OCH_3), 60.5 (4-OCH_3), 115-138.8 (Ar-C), 154.7 (HC=N). MS (ESI, 70 eV) m/z: 371 (M^++1). $C_{19}H_{18}N_2O_4S$. Calculated, % C 61.61, H 4.90, N 7.56. Found, % C 61.65, H 5.96, N 7.51.

N′-(3,4-dimethoxybenzylidene)naphthalene-1-sulfonohydrazide (3c)

Orange solid, mp 150-152 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3260 (NH), 3058 (Ar-H), 2945 (=CH), 1625 (C=N), 1375, 1173 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.73 (s, 6H, OCH_3), 6.75-7.97 (m, 10H, Ar-H), 8.09 (s, 1H, -N=CH-Ar), 8.42 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 56.33 (2C, OCH_3), 115.94-139.64 (Ar-C), 151.52 (HC=N). MS (ESI, 70 eV) m/z: 371 (M^++1). $C_{19}H_{18}N_2O_4S$. Calculated, % C 61.61, H 4.90, N 7.56. Found, % C 61.59, H 5.94, N 7.51.

N′-(3-methoxybenzylidene)naphthalene-1-sulfonohydrazide (3d)

Brown- red solid, mp 142-144 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3265 (NH), 3060 (Ar-H), 2980 (=CH), 1620 (C=N), 1365, 1155 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.75 (s, 3H, OCH_3), 6.82-7.99 (m, 11H, Ar-H), 7.85 (s, 1H, -N=CH-Ar), 8.08 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 56.3 (OCH_3), 114.2- 138.8 (Ar-C), 155.7 (HC=N). MS (ESI, 70 eV) m/z: 341 (M^++1). $C_{18}H_{16}N_2O_3S$. Calculated, % C 63.51, H 4.74, N 8.23. Found, % C 63.45, H 4.79, N 8.28.

N′-(3,4,5-trimethoxybenzylidene)naphthalene-1-sulfonohydrazide (3e)

Red oil, IR (KBr) υ_{max}, cm^{-1}: 3268 (NH), 3085 (Ar-H), 2940 (=CH), 1630 (C=N), 1360, 1160 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.73 (s, 9H, OCH_3), 6.6-7.99 (m, 9H, Ar-H), 7.79 (s, 1H, -N=CH-Ar), 8.45 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 56.3 (3C, OCH_3), 107.9-139.2 (Ar-C), 154.9 (HC=N). MS (ESI, 70 eV) m/z: 401 (M^++1). $C_{20}H_{20}N_2O_5S$. Calculated, % C 59.99, H 5.03, N 7.00 Found, % C 55.92, H 5.07, N 7.05.

N′-(2-methoxybenzyidene)naphthalene-1-sulfonohydrazide (3f)

Yellow powder, mp 144-146 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3270 (NH), 3100 (Ar-H), 2965 (=CH), 1648 (C=N), 1355, 1160 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 3.65 (s, 3H, -OCH_3), 7.23-7.65 (m, 11H, Ar-H), 7.98 (s, 1H, -N=CH-Ar), 8.36 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 122.5-139.2, 156.1 (HC=N). MS (ESI, 70 eV) m/z: 341 (M^++1). Calculated, % C 63.51, H 4.74, N 8.23. Found, % C 63.45, H 4.70, N 8.26.

N′-(3-bromobenzylidene)naphthalene-1-sulfonohydrazide (3g)

Yellow solid, mp 153-155 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3280 (NH), 3095 (Ar-H), 2955 (=CH), 1635 (C=N), 1345, 1150 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 7.24-7.99 (m, 11H, Ar-H), 7.9 (s, 1H, -N=CH-Ar), 8.47 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 122.2-138.8 (Ar-C), 154.8 (=N-CH). MS (ESI, 70 eV) m/z: 390 (M^++2). $C_{17}H_{13}BrN_2O_2S$. Calculated, % C 52.45, H 3.37, N 7.20. Found, % C 52.80, H 3.65, N 7.02.

N′-(3-chlorobenzylidene)naphthalene-1-sulfonohydrazide (3h)

Yellow solid, mp 148-150 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3275 (NH), 3100 (Ar-H), 2960 (=CH), 1640 (C=N), 1340, 1140 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 7.22-7.99 (m, 11H, Ar-H), 7.55 (s, 1H, -N=CH-Ar), 8.54 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 125.4-139.2, 154.7 (HC=N). $C_{17}H_{13}ClN_2O_2S$. MS (ESI, 70 eV) m/z: 346 (M^++1). Calculated, % C 59.21, H 3.80, N 8.12. Found, % C 59.25, H 3.85, N 8.19.

N′-(4-chlorobenzylidene) naphthalene-1-sulfonohydrazide (3i)

Light yellow solid, mp 149-151^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3270 (NH), 3105 (Ar-H), 2952 (=CH), 1645 (C=N), 1360, 1150 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 7.2 (d, 2H, Ar-H), 7.6 (d, 2H, Ar-H), 7.32-7.99 (m, 7H, Ar-H), 7.62 (s, 1H, -N=CH-Ar), 8.22 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 122.5-138.1(m, 7H, Ar-H,), 155.2 (HC=N). MS (ESI, 70 eV) m/z: 346 (M^++1). $C_{17}H_{13}ClN_2O_2S$. Calculated, % C 59.21, H 3.80, N 8.12. Found, % C 59.24, H 3.75, N 8.16.

N′-(2-chlorobenzylidene) naphthalene-1-sulfonohydrazide (3j)

Yellow powders, mp 145-147 ^{0}C. IR (KBr) υ_{max}, cm^{-1}: 3270 (NH), 3100 (Ar-H), 2965 (=CH), 1648 (C=N), 1355, 1160 (SO_2). ^{1}HNMR (300MHz, $CDCl_3$): δ ppm 7.23-7.65 (m, 11H, Ar-H), 7.95 (s, 1H, -N=CH-Ar), 8.42 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 122.5-139.2, 156.1 (HC=N). MS (ESI, 70 eV) m/z: 346 (M^++1). $C_{17}H_{13}ClN_2O_2S$. Calculated, % C 59.21, H 3.80, N 8.12. Found, % C 59.16, H 3.84, N 8.16.

Antibacterial activity

The antibacterial activity of the synthesized compounds 3(a–j) were determined by agar diffusion method against selected Gram-positive and Gram-negative bacteria, *Staphylococcus aureus* (MTCC 3160) and *Escherichia coli* (MTCC 1650) respectively. 100 µl* of broth culture containing test strain was spreaded over the nutrient agar plates. The wells of 6 mm diameter were dug on the nutrient agar plates and filled with the respective test compounds separately. For comparison, DMSO and antibiotic Ampicillin were used as a solvent control and as a reference antibacterial agent, respectively. Triplicate plates of each microorganism were prepared and inoculated plates were then incubated at 37 ± 2 °C for 24 h, and the resulting zones of inhibition (in mm) were measured. The minimum inhibitory concentrations, at which no growth was observed, were taken as the MIC value.

Antifungal activity

The compounds were screened for their antifungal activity on the fungal strains *Aspergillus niger* (MTCC 1781) and *Candida albicans* (MTCC 227). 100 µl* of fungal suspension was spread on Potato Dextrose agar (PDA) plates. The wells of 6 mm diameter were prepared on the inoculated plates and fiof f with respective test compounds separately. For comparison, DMSO and antibiotic Fluconazole were used as solvent control and reference antifungal agent, respectively. Inoculated plates were then incubated at 28 ± 2 °C for 48 h, and the resulting zones of inhibition (in mm) were measured. The minimum inhibitory concentrations at which no fungal growth was observed were recorded as the MIC value.

RESULTS AND DISCUSSION

The synthesis of novel N'-substituted naphthalene-1-sulfonohydrazide derivatives under microwave irradiation was attempted first time. All the reactions proceeded expeditiously within 2-5 min with excellent yields (table 1). Structures of the synthesized compounds were confirmed by elemental analysis and spectral analysis. In compound 3a ^{1}H NMR signal for -CH= proton and –NH- proton appeared as a singlet at 7.73 and 8.15 ppm respectively. Naphthalene ring proton appeared as multiplet in aromatic region at 7.32-7.99 ppm and two doublets for another aromatic ring appeared at 7.39 ppm and 7.80 ppm with 8.1 coupling constant. In ^{13}C NMR, methoxy carbon and imine carbon appeared at 55.3 and 148.53 ppm respectively. All aromatic carbon appeared at 114.2-154.13 ppm. All compounds showed satisfactory elemental analysis.

The mass spectra of compounds showed molecular ion peaks (M+1) confirming their molecular formula.

Table 1: Synthesis of hydrazones under microwave irradiation

Compd.	R_1	R_2	R_3	R_4	Time (Min)	Yield (%)
3a	H	H	OCH_3	H	2 min*(3hr)	90(70)
3b	OCH_3	H	OCH_3	H	2 min*(4hr)	88(65)
3c	H	OCH_3	OCH_3	H	3 min*(4.5hr)	80(65)
3d	H	OCH_3	H	H	3 min*(4hr)	80(60)
3e	H	OCH_3	OCH_3	OCH_3	5 min*(6hr)	78(60)
3f	OCH_3	H	H	H	2 min*(4hr)	85(68)
3g	H	Br	H	H	4 min*(5hr)	82(65)
3h	H	Cl	H	H	4 min*(5hr)	83(60)
3i	H	H	Cl	H	3 min*(4.5hr)	85(65)
3j	Cl	H	H	H	3 min*(5hr)	82(65)

*Time and yield reported in parenthesis were obtained under conventional method

The antimicrobial activities of synthesized compounds were evaluated by determining minimum inhibitory concentration (MIC) values and zone of inhibition (mm). The results of the antimicrobial activity of the synthesized compounds are summarized in table 2. The results revealed that most of the newly synthesized compounds were significantly effective against all tested microbial strains.

Table 2: Antimicrobial activity of compounds
Minimum inhibitory concentration (MIC in µg/ml) and zone of inhibition (mm, given in parenthesis)

Compd.	MIC values in µg/ml (zone of inhibition, mm, mean ± standard deviation)			
	Antibacterial activity		Antifungal activity	
	S. aureus	E. coli	A. niger	C. albicans
a	12.5(12±0.06)	12.5(12±0.11)	25(12±0.08)	25(10±0.01)
b	12.5(12±0.10)	12.5(12±0.02)	25(12±0.20)	25(10±0.12)
c	12.5(12±0.08)	12.5(12±0.04)	25(12±0.30)	25(10±0.14)
d	25(10±0.10)	12.25(14±0.08)	25(12±0.05)	12.5(14±0.30)
e	25(10±0.02)	12.25(14±0.10)	25(12±0.10)	12.5(14±0.08)
f	12.5(14±0.05)	12.5(12±0.07)	25(12±0.15)	25(10±0.20)
g	25(10±0.12)	12.25(14±0.06)	25(12±0.25)	12.5(14±0.16)
h	6.25(12±0.01)	12.5(12±0.09)	12.5(10±0.09)	12.5(12±0.20)
i	6.25(14±0.03)	6.25(14±0.03)	12.5(12±0.12)	12.5(12±0.10)
j	6.25(14±0.07)	12.5(12±0.08)	25(10±0.02)	25(10±0.05)
Ampicillin	6.25(20)	6.25(18)	-	-
Fluconazole	-	-	12.5(20)	6.25(18)

N=triplicate, Valuses should be in mean±SD as per experiment size.

CONCLUSION

In conclusion, we have developed a simple, mild rapid and one step green method for the synthesis of a novel series of *N'-(substitutedbenzylidene)naphthalene-1-sulfonohydrazide* derivatives under microwave irradiation and screened for their antimicrobial activity. All compounds showed good to excellent microbial activity against all tested microbial strains, which are also interesting for future scope to be used as templates for generating better antibacterial and antifungal lead molecules.

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CONFLICT OF INTERESTS

Declared None

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